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# Design and initiation of a study to assess the direct and indirect effects of influenza vaccine given to children in rural India

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## Abstract

The burden of disease due to influenza is not well characterized for children in developing countries and the effectiveness of available influenza vaccines in lower resource settings has not been established. We initiated a prospective, longitudinal, phase IV, household-randomized, controlled, observer-blinded three year study (2009–2011) in a rural community of India to measure the total and indirect household protective effects of immunizing children ages 6 months through 10 years with seasonal inactivated trivalent influenza vaccine (TIV) or a control vaccine ($n$ = 3697). Active weekly surveillance was conducted year round with home visits for identification of febrile acute respiratory illness (FARI) conducted for all vaccine recipients and household members ($n$ = 18,220). Nasal and throat swabs were collected from each FARI episode for influenza detection by real-time reverse transcription polymerase chain reaction. The primary outcome was reduction in laboratory confirmed influenza infections in the influenza vaccine versus control vaccine group, with secondary outcome assessing indirect effects among the entire study population. This report describes the study site, cluster study design, choice of study and control vaccines, and the initial enrollment in the study.

### Keywords

Influenza; Vaccine; Developing country; India; Child

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**Conflict of interest**

The authors declare no conflict of interest.

## 1. Introduction

Although influenza disease is well characterized in both developed and developing countries, the epidemiology in developing countries is less well described, particularly for children [1–3]. Furthermore, influenza vaccine use remains very limited in many developing countries and the benefits of immunization in these populations have not been investigated to the same extent as in developed countries [4]. Policy makers may have concerns as to whether the potential benefits justify the cost and difficulties associated with adding a vaccine to their national schedules. This is particularly relevant because in contrast to the single or limited series of immunizations required by most childhood vaccines, influenza vaccines are given annually. In addition, the issue of indirect immunity has not been addressed in a developing country, where various factors, including malnutrition, overcrowding and inadequate sanitation may influence the degree of protection [5,6]. Lastly, understanding direct and indirect effects of influenza vaccine in these settings will help optimize deployment of vaccine in the face of pandemic influenza threats.

Among children less than 5 years of age in India, there are 43 million episodes of pneumonia and over 400,000 pneumonia deaths each year [7]. In the area in which the current study is ongoing, 11% of acute lower respiratory infections in young children are due to influenza [8].

India is considering adding new vaccines such as that for influenza to its vaccine program. National policy states that new vaccines would be considered based disease burden as well as on safety and efficacy of the vaccine [9]. Moreover, vaccine manufacturers in India have begun production of influenza vaccine.

The objectives of the current study are to measure the efficacy of influenza vaccine in reducing influenza infections among immunized children and the indirect protective effects for unvaccinated persons in the households of immunized children. Here we report the salient aspects of the planning, design, and initiation of this ongoing study in India.

## 2. Methods

### 2.1. Study site and population

The study site was in Ballabgarh, located in Faridabad in the state of Haryana in northern India. Three villages (Dayalpur, Atali, and Chandawli) were selected on the basis of sample size requirements, presence of a health facility, and proximity to the Ballabgarh health center. The study design and initial participation are described here, efficacy results will be reported later. Health care at the site was provided by the Comprehensive Rural Health Services Project (CRHSP), a collaborative effort between the Centre for Community Medicine at the All India Institute of Medical Sciences (AIIMS) in New Delhi and the state of Haryana. Each person in the catchment area was recorded in the CRHSP computerized database and has a unique health information system number. In the study villages many homes were in compounds that shared a courtyard which likely resulted in numerous interactions of children and adults. The extent of social interaction and mixing within the

compound seemed the most important attributes for the purposes of this study, thus all of those within a compound were considered as one household for randomization [10,11].

### 2.2. Study design

The study is prospective, controlled, participant and observer blinded and randomized by household. The allocation as to vaccine group was permanent for the entire study, each year children assigned to receive influenza vaccine will receive influenza vaccine and those assigned to the control poliovirus vaccine will receive poliovirus vaccine.

### 2.3. Sample size estimations

Power calculations were performed for both total (direct and indirect) protection of immunized children as well as indirect protection of unimmunized individuals in the households of immunized children (Table 1). For the total effect among children, it was assumed that the laboratory confirmed influenza attack rate would be 5% per year (or 5 per 100 person/years) in the unvaccinated group, and we decided the minimum detectable effectiveness should be 50% [12]. To assess total protection, 785 households are required per study group for 95% power. This was based on a conservative assumption of a coefficient of variation of 0.25 for the rates [13]; with about 2 vaccine-eligible children per household, only a small proportion of households were expected to have more than one confirmed child case, with resulting low within-household correlation.

For the indirect effects, the level of protection was difficult to predict [14]. A recent study reported an indirect protective effect of 61% for influenza immunization, similar to the direct protective effect [6]. We anticipated the majority of the indirect protective effect occurs in the home and will be near or exceed 25%, which we judged would be a minimum effect of public health importance. With 893 households per group the study would have 80% power for 25% effectiveness (Table 1).

### 2.4. Enrollment, inclusion and exclusion criteria

Subjects were approached in their homes and offered enrollment. All inhabitants of the three study villages were eligible to participate in the surveillance component of the study. There were no exclusion criteria for surveillance. Participation in the vaccine arm of the study was available to children 6 months through 10 years of age. Exclusion criteria from the vaccine groups included known allergy to eggs, hypersensitivity to the vaccines or components of the vaccines, acute severe febrile illness (temporary exclusion) or any other condition that would impose a health risk.

### 2.5. Randomization and blinding

Household randomization to TIV or IPV was performed by the study statistician and vaccine assignments were indicated in a coded fashion. All of those living within a compound were considered as one household for randomization. Labels were applied that showed the vaccine code and obscured the underlying labels of the pre-filled vaccine syringes (as suggested by personal communication, John Victor). The pharmacist did not participate in field activities or vaccine administration. Separate vaccine administrators were hired solely for the immunization period.

## 3. Vaccination

Seasonal inactivated split-virion trivalent influenza vaccine (TIV) and trivalent inactivated poliovirus vaccine (IPV) are commercially available in India [15]. Oral poliovirus vaccine (OPV) is the vaccine in use to control poliovirus in India. However, the Indian Academy of Pediatrics recommends the addition of IPV to OPV [16]. Vaccine schedules and composition are shown (Table 2). At the initiation of the study only northern hemisphere influenza vaccine was available in India, it became available in the fall each year. Immunizations were accomplished December 2009–January 2010 (year 1), and in October–November of 2010 and 2011.

### 3.1. Case definition: febrile acute respiratory illness (FARI)

FARI was used as the clinical indicator of possible influenza infection and was defined as reported fever and any respiratory complaint (such as cough, sore throat, nasal congestion, runny nose, earache, or difficulty breathing) within the past week. No documentation of fever or observation of other signs was required. We believed this provided increased sensitivity for identification of influenza illnesses, albeit at the expense of lower specificity [17]. However, because the primary outcome measure was laboratory confirmed influenza, the final measure is very specific. Each FARI episode was considered to last a maximum of two weeks.

### 3.2. Surveillance

Active surveillance was performed with weekly visits to the homes. Both vaccine and non-vaccine participants were enrolled and under surveillance. Households that did not include vaccinees were expected to provide additional data as to the role of children in introducing influenza into their homes and risk factors for influenza. When FARI was reported subjects were assessed and temperature, respiratory rate, heart rate, pulse oximetry, and respiratory effort were recorded. FARI events were classified by World Health Organization criteria [18,19]. If national standards required therapy it was provided or the individuals were referred to the health center. As our data showed there may be year round circulation and bimodal peaks of influenza activity surveillance occurred year around [20].

### 3.3. Sample collection and processing

From each patient with FARI a throat and nasal swab were collected (nasopharyngeal swabs alone in infants). Samples were divided into aliquots, for influenza detection, viral culture, and storage. CDC real time RT-PCR protocols were used as described for influenza testing, these assays are highly sensitive and specific [21]. Prior to initiation of testing AIIMS laboratory staff received CDC training and the laboratory underwent external quality control assessments. Further antigenic characterization of the viruses was planned to include hemagglutination inhibition.

### 3.4. Data management

Creation of the study databases consisted of a linkage of three databases: (1) an electronic Rural Health Information System database with house numbers and demographic data for enrolled residents; (2) structured paper forms used for field data collection that were

optimized for optical character recognition scanning for rapid processing using TeleForm® software (Autonomy Inc., San Francisco, CA) and high speed scanners; and (3) an in-house created laboratory data base that stored all study sample testing and laboratory results. All sources of the data were uploaded to a secured study server that resides in India, where data could be downloaded and processed by the appropriate study staff both in India and in the USA. All forms that were scanned also had select data fields that were human verified while processing through TeleForm® software for data quality. All data were linked and processed for data quality, both individually and across data sources. Study data were maintained in SAS® (SAS Systems, Inc., Cary, NC) databases for data editing, maintenance and analyses.

### 3.5. Analysis plan

The main statistical analyses proposed are total vaccine efficacy among children 6 months–10 years of age and indirect vaccine efficacy among non-vaccinated household contacts of children enrolled for vaccination [22]. Statistical significance in all our analyses will be determined using a two-sided 0.05 significance level. Statistical analyses will be conducted on a year-to-year basis as well as pooled analysis for multiple years. For the children 6 months–10 years of age, analyses will be modified intention-to-treat, comparing those children who actually receive a dose of influenza vaccine (intervention households) to those receiving control vaccine (control households). Analyses of older household members will be strict intention-to-treat, in that their experience will be analyzed according to the allocation of the household. The influenza-vaccinated (those who receive at least one dose) and control vaccine individuals will be compared with respect to incidence of FARI and laboratory confirmed influenza. Vaccine efficacy will be estimated for children from 6 months through 10 years of age using incidence density methods. Incidence rates of laboratory confirmed influenza among influenza and control vaccine recipients will be determined by dividing the sum of laboratory confirmed influenza episodes/total number of person weeks at risk. The unadjusted rate ratio (RR) of influenza will be calculated, and total vaccine efficacy calculated as $(1 - RR) \times 100\%$. 95% confidence intervals will be calculated, accounting for within-household correlation by conditioning on the total number of episodes and assuming a Poisson model with Pearson residual-estimated scale parameter [23]. Similarly, rates among individuals aged 11 years and old will be compared between intervention-assigned households and control-assigned households, which will yield estimates of the indirect effect of the intervention. For analyses in which more than 10% of the individuals experience more than one outcome event, we can gain further precision by using a generalized linear mixed model (Poisson regression with random effects) to account for the two levels (household and individual) of correlation.

### 3.6. Ethical approvals

Ethical review was provided by the AIIMS Ethics Committee and the University of Alabama Birmingham (UAB) Institutional Review Board. The Centers for Disease Control and Prevention (CDC) Institutional Review Board approved a request to rely upon the AIIMS Ethics Committee review. The Health Ministry Steering Committee of the Indian Council for Medical Research provided federal government review and approval. A Data and Safety Monitoring Board was established In Delhi to assess the safety of the participants. The trial

was enrolled in Clinical Trials Registry – India (CTRI/2010/091/001235,13-10-2010) and at ClinicalTrials.gov (NCT00934245).

Prior to seeking informed consent meetings were undertaken with village leaders and village grass-roots workers. Adults provide signed consent, for children parental consent was obtained, and for children 7 years of age and up assent was requested.

## 4. Results

High rates of enrollment were obtained for both surveillance and vaccine activities, over 90% of the eligible population agreed to participate in surveillance (Table 3). Similarly, in the first year of immunization (November 2009–January 2010) among 3694 vaccine eligible children 80% were vaccinated completely (one or two doses depending on age) and 11% received one of two planned doses of vaccine (Fig. 1). Enrollment and vaccine participation numbers were provisional at this time as data analysis was ongoing. Two thousand eight hundred and six households enrolled in the study, of which 1690 households included children eligible to participate in the vaccine component. This provided 845 households for each of the two study arms, influenza and control vaccine. This met the sample size goal for direct effects (785 households) and was near the goal for assessing indirect effects (893 households), as well as the goals for individual subjects as described in Methods (Table 1).

## 5. Discussion

This report describes the design and initiation of a study to define the indirect and total protective effects of immunizing children with trivalent influenza vaccine (TIV) in a rural community of India. The study site in Ballabgarh builds on the commitment to research from the AIIMS faculty members who provide primary care in the CRHSP and their rapport among the study population. The investigators at AIIMS, UAB, and the CDC were familiar with the study population and had established relationships that facilitated implementation of the study [8].

Cluster designs are essential for the assessment of indirect immunity following immunization [24]. Household randomization was chosen as it provided a sufficient number of units of randomization and kept the number of participants within the limits of available resources. Randomization at the individual level would have limited the possibility of detecting indirect protection in situations where there was more than one child in the house and not all the children received influenza vaccine. A limitation of the use of households for randomization was that it reduced the potential contribution of community level indirect effects, since not all the children in each village will receive influenza vaccine. However, CDC was collaborating on a village randomized trial in Senegal and that would provide useful information on community level effects.

There were several factors to consider in choosing a control vaccine. Age, route, and timing of administration needed to be compatible with that of the study vaccine. The control vaccine also needed to be licensed in India and not be given as a routine immunization. The control vaccine also should not interfere with the assessment of outcomes for the study. Pneumococcal, *haemophilus influenzae* B and hepatitis B vaccines were considered and then

rejected on one of the above grounds. Inactivated poliovirus vaccine was chosen as a vaccine that satisfied the above requirements. Furthermore, it was recommended for use in India as an adjunct to the national approach using oral poliovirus vaccine [16].

Influenza virus infections are frequently but not always associated with fever and respiratory symptoms [17]. This has been confirmed in another investigation in the study area, where influenza case definitions failed to identify all hospitalized patients who were infected with influenza virus (unpublished data, Vivek Gupta et al.). Thus our clinical criteria would not result in testing in all influenza infections. Similarly, and especially in young children, influenza might manifest as fever without other symptoms [25]. These cases too would not be identified in our study. As a practical matter, definitions such as FARI or influenza like illness are frequently used in clinical investigations of influenza.

A related issue is that the likelihood of a positive test for influenza declines over time. Peak virus shedding in volunteers occurs 2 days after virus challenge and usually stops by 7 days [26]. Therefore, weekly visits in this study might result in samples being taken when virus shedding had decreased. Although clinical case definitions for influenza have limitations, we attempted to balance these parameters by using a subjective case definition combined with a highly sensitive and specific virus diagnostic technique [17].

The efficacy of influenza vaccine depends in part on the antigenic match between the viruses in circulation vs. those used to make the vaccine [15]. The appearance of influenza A(H1N1)pdm09 in India posed a challenge as the seasonal vaccine formulation did not include the pandemic virus and monovalent influenza A(H1N1)pdm09 vaccine was not yet available in India. The pandemic provided a dramatic example of antigenic mismatch between the circulating virus and the vaccine components and emphasized the importance of multi-year studies of influenza vaccines. It also required a change to two doses of vaccine in 2010 as compared to the planned single dose of vaccine.

Northern hemisphere influenza vaccine is imported into India and administered in the fall. The study described here used the northern hemisphere formulation. However, recent surveillance data showed the largest peak of influenza is in July–September during the rainy season in the Delhi region, with minor peaks in the winter [20]. Indian regions where influenza occurs during the rainy season might benefit from immunization before the summer using the southern hemisphere influenza vaccine due to timing of availability. Furthermore, for influenza viruses that are not well matched antigenically to the components of the vaccine, there may reduced efficacy for TIV more than four months after immunization [27]. This suggests immunization closer in time to the rainy season influenza period may offer advantages as compared to immunization in the fall of the preceding year. In recognition of this pattern of seasonality, we plan a future study of immunization in spring with southern hemisphere influenza vaccine so that these results can be as compared with the current study of fall immunization with northern hemisphere influenza vaccine.

## 6. Conclusions

This report describes the design of an influenza vaccine study being undertaken among children in rural India. The study should provide valuable new data as to the potential role of influenza vaccines for the reduction of influenza virus disease burden in developing countries.

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*Contributors:* All authors were involved at study conception and design stage and/or acquisition of data and interpretation of data; draft/critical revision of the article and final approval of the manuscript.

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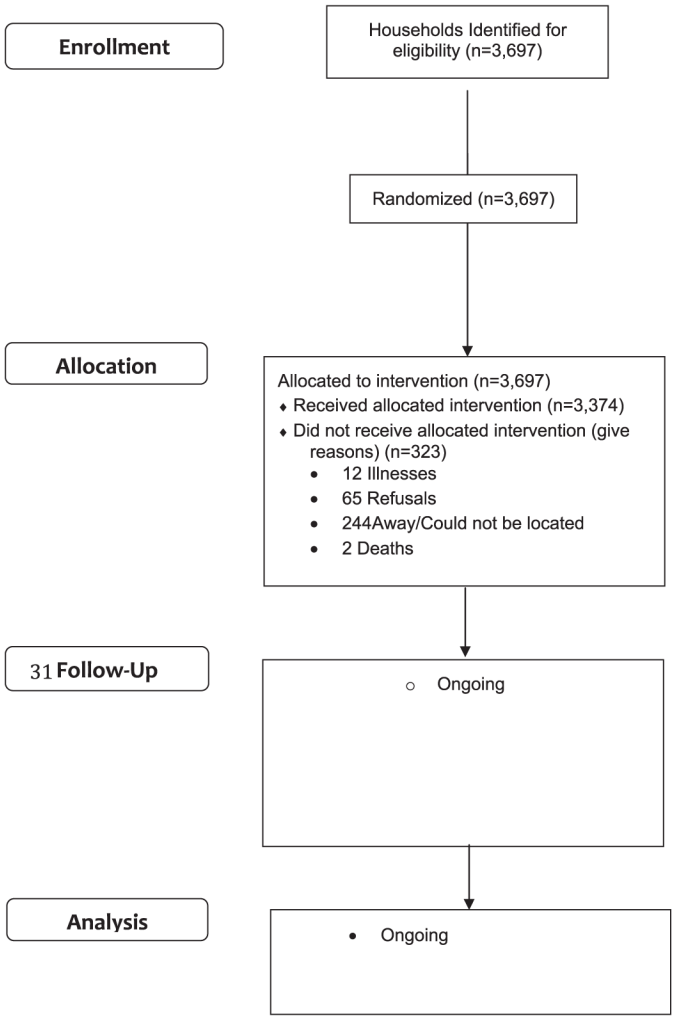


**Fig. 1.**
Flow diagram of enrollment for participation in vaccine component of study.

**Table 1**

Total and indirect effect sample size estimates.

| | Total (assumes 50% protection) | Indirect (assumes 25% protection) |
|---|---|---|
| Control group rate per 100 child-years | 5 | 5 |
| Vaccine group rate per 100 child-years | 2.5 | 3.75 |
| Vaccine efficacy | 50% | 25% |
| Coefficient of variation | 0.25 | 0.25 |
| Cluster Size | 2 | 5 |
| Power | 95% | 80% |
| Number of households required (clusters) | 785 | 893 |
| Subjects per group | 1570 | 4465 |

## Table 2

Vaccine doses and schedule.

| Age | Dose | # Doses year 1 | # Planned doses years 2 and 3 |
|---|---|---|---|
| Influenza vaccine | | | |
| 6–35 months | 0.25 ml[a] | 2 | 1 |
| 3–8 years | 0.5 ml[b] | 2 | 1 |
| 9–10 years | 0.5 ml[b] | 1 | 1 |
| Poliovirus vaccine[c] | | | |
| 6 months–8 years | 0.5 ml | 2 | 1 |
| 9–10 years | 0.5 ml | 1 | 1 |

The strains for the 2009–2010 influenza vaccine were: A/Brisbane/59/2007 (H1N1), A/Brisbane/10/2007 (H3N2)-like strain A/Uruguay/716/2007, and B/Brisbane/60/2008.

[a] VAXIGRIP Junior.

[b] VAXIGRIP.

[c] Imovax Polio, Sanofi Pasteur India, New Delhi.

**Table 3**

Age and gender of population enrolled in surveillance.

| Age | Total # (%) | Male/female (ratio) |
|---|---|---|
| 0–5 years | 2510 (13.8) | 1362/1148 (1.12) |
| 6–18 years | 4714 (25.9) | 2574/2140 (1.2) |
| 19–29 years | 4068 (22.3) | 2070/1998 (1.04) |
| 30–44 years | 3693 (20.3) | 2023/1670 (1.21) |
| 45–59 years | 1985 (10.9) | 999/986 (1.01) |
| 60+ years | 1250 (6.8) | 584/666 (0.88) |
| Total | 18,220 | 9612/8608 (1.12) |